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|---|---|---|
| NEWS 1 | | Web Page URLs for STN Seminar Schedule - N. America |
| NEWS 2 | | "Ask CAS" for self-help around the clock |
| NEWS 3 | JAN 17 | Pre-1988 INPI data added to MARPAT |
| NEWS 4 | FEB 21 | STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results |
| NEWS 5 | FEB 22 | The IPC thesaurus added to additional patent databases on STN |
| NEWS 6 | FEB 22 | Updates in EPFULL; IPC 8 enhancements added |
| NEWS 7 | FEB 27 | New STN AnaVist pricing effective March 1, 2006 |
| NEWS 8 | MAR 03 | Updates in PATDPA; addition of IPC 8 data without attributes |
| NEWS 9 | MAR 22 | EMBASE is now updated on a daily basis |
| NEWS 10 | APR 03 | New IPC 8 fields and IPC thesaurus added to PATDPAFULL |
| NEWS 11 | APR 03 | Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL |
| NEWS 12 | APR 04 | STN AnaVist $500 visualization usage credit offered |
| NEWS 13 | APR 12 | LINSPEC, learning database for INSPEC, reloaded and enhanced |
| NEWS 14 | APR 12 | Improved structure highlighting in FQHIT and QHIT display in MARPAT |
| NEWS 15 | APR 12 | Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected |
| NEWS 16 | MAY 10 | CA/CAplus enhanced with 1900-1906 U.S. patent records |
| NEWS 17 | MAY 11 | KOREAPAT updates resume |
| NEWS 18 | MAY 19 | Derwent World Patents Index to be reloaded and enhanced |
| NEWS 19 | MAY 30 | IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2 |
| NEWS 20 | MAY 30 | The F-Term thesaurus is now available in CA/CAplus |
| NEWS 21 | JUN 02 | The first reclassification of IPC codes now complete in INPADOC |
| NEWS EXPRESS | | FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT http://download.cas.org/express/v8.0-Discover/ |
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| NEWS X25 | | X.25 communication option no longer available after June 2006 |

Enter NEWS followed by the item number or name to see news on that specific topic.

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FILE 'HOME' ENTERED AT 12:25:21 ON 22 JUN 2006

=> file medline, uspatful, dgene, embase, wpids, hcaplus, biosis, biotechds
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                                                             ENTRY    SESSION
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FILE 'USPATFULL' ENTERED AT 12:26:14 ON 22 JUN 2006
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=> s protamine
L1        33448 PROTAMINE

=> s l1 and (heparin inactivation)
L2           16 L1 AND (HEPARIN INACTIVATION)

=> d l2 ti abs ibib tot

L2   ANSWER 1 OF 16     MEDLINE on STN
TI   [Amino acid composition, heterogeneity and antiheparin activity of
     protamine sulfate from the milt roe of the sturgeon Acipenser
     sturio].
     Aminokislotnyi sostav, geterogennost' i antigeparinovaia aktivnost'
     protamina sul'fata molok osetra Acipenser sturio.
AB   The homogeneous preparation of protamine sulphate is obtained
     chromatographically and electrophoretically from milt roe of the sturgeon.
     Its amino acid composition and properties are studied.  The methods to
     blockade the functional groups of protamine sulphate amino acids
     is used to investigate the possible mechanism of heparin
     inactivation.
ACCESSION NUMBER:   90208925     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 2631325
TITLE:              [Amino acid composition, heterogeneity and antiheparin
                    activity of protamine sulfate from the milt roe
                    of the sturgeon Acipenser sturio].
                    Aminokislotnyi sostav, geterogennost' i antigeparinovaia
                    aktivnost' protamina sul'fata molok osetra Acipenser
                    sturio.
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| AUTHOR: | Borodinskaia I N; Mishunin I F |
| SOURCE: | Ukrainskii biokhimicheskii zhurnal, (1989 Nov-Dec) Vol. 61, No. 6, pp. 84-8.<br>Journal code: 7804246. ISSN: 0201-8470. |
| PUB. COUNTRY: | USSR |
| DOCUMENT TYPE: | Journal; Article; (JOURNAL ARTICLE) |
| LANGUAGE: | Russian |
| FILE SEGMENT: | Priority Journals |
| ENTRY MONTH: | 199005 |
| ENTRY DATE: | Entered STN: 1 Jun 1990<br>Last Updated on STN: 1 Jun 1990<br>Entered Medline: 2 May 1990 |

L2 ANSWER 2 OF 16 USPATFULL on STN

TI Coated surfaces for immobilizing negatively charged anticoagulating agents from blood fluid

AB A wound closure apparatus is provided which utilizes blood fluid by activating the clotting cascade of blood fluid outside the body within a substantially enclosed sterile container then introducing, the blood fluid to the wound site to complete clotting. An apparatus for providing ways of inhibiting anticoagulating agents, and slowing fibrin clot degradation are also disclosed. Kits for practicing the invention singularly or in combination with, and/or associated with preferred procedures are also disclosed. The invention provides a clotting cascade initiation apparatus (1) including a substantially enclosed sterile containment chamber within which an aliquot of blood fluid, either autologous or from donor sources can be received, and retained. In preferred embodiments, the sterile containment chamber further includes a heparin binding agent which will bind heparin and remove it from the blood fluid. In further embodiments, the containment chamber will also include a procoagulating agent, wherein a clotting cascade can be initiated when the blood fluid is accepted into the sterile containment chamber.

| | |
|---|---|
| ACCESSION NUMBER: | 2003:325393 USPATFULL |
| TITLE: | Coated surfaces for immobilizing negatively charged anticoagulating agents from blood fluid |
| INVENTOR(S): | Sandhu, Shivpal S., Reading, UNITED KINGDOM |
| PATENT ASSIGNEE(S): | BioInteractions Ltd. (non-U.S. corporation) |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2003229376 | A1 | 20031211 |
| APPLICATION INFO.: | US 2003-389696 | A1 | 20030314 (10) |

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-291965, filed on 12 Nov 2002, PENDING Continuation of Ser. No. US 2002-194403, filed on 11 Jul 2002, PENDING Continuation of Ser. No. US 2000-585488, filed on 1 Jun 2000, GRANTED, Pat. No. US 6482223

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1999-136837P | 19990601 (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | APPLICATION |
| LEGAL REPRESENTATIVE: | Brad Pedersen, Patterson, Thuente, Skaar & Christensen, P.A., 4800 IDS Center, 80 South 8th Street, Minneapolis, MN, 55402-2100 |
| NUMBER OF CLAIMS: | 15 |
| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 4 Drawing Page(s) |
| LINE COUNT: | 992 |

L2 ANSWER 3 OF 16 USPATFULL on STN
TI Clotting cascade initiating apparatus and methods of use
AB Wound closure methods and apparatus are provided which utilize blood fluid by activating the clotting cascade of blood fluid outside the body within a substantially enclosed sterile container then introducing the blood fluid to the wound site to complete clotting. Methods and apparatus for providing ways of inhibiting anti-coagulating agents and slowing fibrin clot degradation are also disclosed. Kits for practicing the invention singularly or in combination with and/or associated with preferred procedures are also disclosed. The present invention provides improved methods of creating hemostasis or control of bleeding at the site of wounds, particularly wounds created in arteries during procedures employing percutaneous access. The invention preferably includes the steps of acquiring an aliquot of a patient's blood, i.e., autologous blood, removing a negatively charged anti-coagulating agent, preferably heparin, from the blood, and preferably initiating the blood's natural clotting cascades and transporting the thus treated blood to the site of the wound where the clotting cascade will be completed producing a clot at the wound site that will create a condition of hemostasis. The invention further provides a clotting cascade initiation apparatus including a substantially enclosed sterile containment chamber within which an aliquot of blood fluid, either autologous or from donor sources, can be received and retained. In preferred embodiments, the sterile containment chamber further includes a heparin binding agent which will bind heparin and remove it from the blood fluid. In further embodiments the containment chamber will also include a procoagulating agent, wherein a clotting cascade can be initiated when the blood fluid is accepted into the sterile containment chamber.

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|---|---|
| ACCESSION NUMBER: | 2003:100490 USPATFULL |
| TITLE: | Clotting cascade initiating apparatus and methods of use |
| INVENTOR(S): | Nowakowski, Karol L., Circle Pines, MN, UNITED STATES<br>Olson, James E., Eagan, MN, UNITED STATES<br>Joseph, Edward T., Inver Grove Heights, MN, UNITED STATES<br>Ericson, Daniel G., Rochester, MN, UNITED STATES |
| PATENT ASSIGNEE(S): | Closys Corporation (U.S. corporation) |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2003069601 | A1 | 20030410 |
| APPLICATION INFO.: | US 2002-291965 | A1 | 20021112 (10) |

| | |
|---|---|
| RELATED APPLN. INFO.: | Continuation of Ser. No. US 2000-585488, filed on 1 Jun 2000, GRANTED, Pat. No. US 6482223 Continuation-in-part of Ser. No. US 1998-212080, filed on 15 Dec 1998, GRANTED, Pat. No. US 6159232 |
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | APPLICATION |
| LEGAL REPRESENTATIVE: | Robert C. Freed, MOORE & HANSEN, 2900 Wells Fargo Center, 90 South Seventh Street, Minneapolis, MN, 55402 |
| NUMBER OF CLAIMS: | 20 |
| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 4 Drawing Page(s) |
| LINE COUNT: | 1102 |

L2 ANSWER 4 OF 16 USPATFULL on STN
TI Clotting cascade initiating apparatus and methods of use
AB Wound closure methods and apparatus are provided which utilize blood fluid by activating the clotting cascade of blood fluid outside the body within a substantially enclosed sterile container then introducing the blood fluid to the wound site to complete clotting. Methods and

apparatus for providing ways of inhibiting anti-coagulating agents and slowing fibrin clot degradation are also disclosed. Kits for practicing the invention singularly or in combination with and/or associated with preferred procedures are also disclosed. The present invention provides improved methods of creating hemostasis or control of bleeding at the site of wounds, particularly wounds created in arteries during procedures employing percutaneous access. The invention preferably includes the steps of acquiring an aliquot of a patient's blood, i.e., autologous blood, removing a negatively charged anti-coagulating agent, preferably heparin, from the blood, and preferably initiating the blood's natural clotting cascades and transporting the thus treated blood to the site of the wound where the clotting cascade will be completed producing a clot at the wound site that will create a condition of hemostasis. The invention further provides a clotting cascade initiation apparatus including a substantially enclosed sterile containment chamber within which an aliquot of blood fluid, either autologous or from donor sources, can be received and retained. In preferred embodiments, the sterile containment chamber further includes a heparin binding agent which will bind heparin and remove it from the blood fluid. In further embodiments the containment chamber will also include a procoagulating agent, wherein a clotting cascade can be initiated when the blood fluid is accepted into the sterile containment chamber.

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|---|---|
| ACCESSION NUMBER: | 2002:303578 USPATFULL |
| TITLE: | Clotting cascade initiating apparatus and methods of use |
| INVENTOR(S): | Nowakowski, Karol L., Circle Pines, MN, United States<br>Olson, James E., Eagan, MN, United States<br>Joseph, Edward T., Inver Grove Heights, MN, United States<br>Ericson, Daniel G., Rochester, MN, United States |
| PATENT ASSIGNEE(S): | Closys Corporation, Edina, MN, United States (U.S. corporation) |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 6482223 | B1 | 20021119 |
| APPLICATION INFO.: | US 2000-585488 | | 20000601 (9) |
| RELATED APPLN. INFO.: | Continuation-in-part of Ser. No. US 1998-212080, filed on 15 Dec 1998, now patented, Pat. No. US 6159232 | | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1997-69834P | 19971216 (60) |
| | US 1999-136837P | 19990601 (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | GRANTED |
| PRIMARY EXAMINER: | Jackson, Gary |
| LEGAL REPRESENTATIVE: | Moore & Hansen |
| NUMBER OF CLAIMS: | 19 |
| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 5 Drawing Figure(s); 4 Drawing Page(s) |
| LINE COUNT: | 1095 |

L2 ANSWER 5 OF 16 USPATFULL on STN

TI Process and device for the specific adsorption of heparin

AB A process for the specific adsorption of heparin and other heparin-like substances which comprises flowing a buffered solution of whole blood, from which corpuscular blood constituents have been removed, plasma and/or solutions containing whole blood or plasma through an adsorber capsule containing a medium that adsorbs heparin and other heparin-like substances at an acid pH, preferably in the range of 4.0 to 5.5.

Preferably, the process is carried out in a closed, extracorporeal circulation and the medium possesses anion exchange resin properties.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | |
|---|---|
| ACCESSION NUMBER: | 90:48589 USPATFULL |
| TITLE: | Process and device for the specific adsorption of heparin |
| INVENTOR(S): | Seidel, Dietrich, Gottingen, Germany, Federal Republic of<br>Feller, Wolfgang, Melsungen, Germany, Federal Republic of<br>Rosskopf, Gerhard, Fuldabruck-Dornhagen, Germany, Federal Republic of |
| PATENT ASSIGNEE(S): | B. Braun-SSC AG, Emmenbrucke, Switzerland (non-U.S. corporation) |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 4935204 | | 19900619 |
| APPLICATION INFO.: | US 1988-271368 | | 19881114 (7) |
| RELATED APPLN. INFO.: | Continuation of Ser. No. US 1988-149905, filed on 28 Jan 1988, now abandoned which is a continuation of Ser. No. US 1985-744197, filed on 13 Jun 1985, now abandoned | | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | DE 1984-3422494 | 19840616 |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | Granted |
| PRIMARY EXAMINER: | Rollins, John W. |
| LEGAL REPRESENTATIVE: | Kenyon & Kenyon |
| NUMBER OF CLAIMS: | 35 |
| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 1 Drawing Figure(s); 1 Drawing Page(s) |
| LINE COUNT: | 798 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN

TI Point of care heparin determination system

AB Methods and devices for point of care determination of heparin concentration in blood are described. Cartridges including **protamine** ion sensitive electrodes (ISEs) and reference electrodes and systems for automatically determining heparin concentration in the cartridges are provided. Some systems add blood to a **protamine** bolus sufficient to bind all heparin, leaving excess **protamine**. The excess **protamine** concentration can be determined by measuring the initial slope of the electrode potential rate of change, and comparing the slope to known **protamine** concentration slope values. In some cartridges, an oscillating pressure source moves the blood-**protamine** mixture back and forth across the **protamine** ISE. Some systems also use a second blood sample having the heparin removed or degraded to create a blank reference sample. **Protamine** ISEs can include polyurethane polymer, DNNS ionophore, and NPOE plasticizer. The polyurethane may include hard segments and soft segments, where both hard and soft segments may include cyclic and straight chain aliphatic moieties having essentially no ester or ether groups. Some hard segments may include methylene di-Ph groups. Some reference electrodes have the same polymer, plasticizer, and ionophore as the measurement electrode, but with a different concentration of ionophore.

| | |
|---|---|
| ACCESSION NUMBER: | 2005:1290201 HCAPLUS |
| DOCUMENT NUMBER: | 144:19185 |

TITLE: Point of care heparin determination system
INVENTOR(S): Bonnema, Kelvin; Hobot, Christopher M.; Meyer, Randy; Nippoldt, Douglas D.; Qin, Wei; Ramamurthy, Narayanan; Sitko, Vitally G.; Ye, Qingshan
PATENT ASSIGNEE(S): Medtronic, Inc., USA
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005116623 | A2 | 20051208 | WO 2005-US16463 | 20050511 |
| WO 2005116623 | A3 | 20060126 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2006016701 | A1 | 20060126 | US 2005-126887 | 20050511 |
| PRIORITY APPLN. INFO.: | | | US 2004-572071P P | 20040517 |

L2 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
TI Amino acid composition, heterogeneity and antiheparin activity of **protamine** sulfate from milt of the sturgeon Acipenser sturio
AB A homogeneous preparation of **protamine** sulfate was obtained chromatog. and electrophoretically from milt of the sturgeon A. sturio. Its amino acid composition and properties were studied. Chemical blockage of functional groups of **protamine** sulfate amino acids was used to investigate the possible mechanism of **heparin inactivation**. The results were consistent with previous findings that arginine, lysine, and histidine residues in **protamine** sulfate interact with thiol groups in heparin.
ACCESSION NUMBER: 1990:32337 HCAPLUS
DOCUMENT NUMBER: 112:32337
TITLE: Amino acid composition, heterogeneity and antiheparin activity of **protamine** sulfate from milt of the sturgeon Acipenser sturio
AUTHOR(S): Borodinskaya, I. N.; Mishunin, I. F.
CORPORATE SOURCE: A. V. Palladin Inst. Biochem., Kiev, USSR
SOURCE: Ukrainskii Biokhimicheskii Zhurnal (1978-1999) (1989), 61(6), 84-8
CODEN: UBZHD4; ISSN: 0201-8470
DOCUMENT TYPE: Journal
LANGUAGE: Russian

L2 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
TI Influence of platelet factor 4 on the neutralization of heparin by **protamine**
AB Blood platelet factor 4 (PF4) is comparable to **protamine** sulfate in the in vitro neutralization of heparin, but the complexes formed with heparin are different. Even with an excess of PF4, no large PF4-heparin complexes are formed and none of the complexes are able to activate antithrombin III (ATIII), nor do these complexes dissociate during incubation

in plasma at 37°. The action of PF4 and **protamine** is complementary, but excess **protamine** displaces PF4 or prevents its complexes with heparin. When excess **protamine** is used to neutralize heparin in the presence of PF4, large heparin-**protamine** complexes are formed incorporating PF4. In contrast to the heparin-**protamine** complexes formed without PF4, these do not activate ATIII nor do they dissociate on incubation. Since PF4 is liberated during extracorporeal bypass procedures, it contribution to the stability of heparin-**protamine** complexes in vivo may influence the amount of **protamine** needed to neutralize heparin as well as affect the reactions which have been reported on injection of **protamine** after the procedures.

ACCESSION NUMBER: 1989:490155 HCAPLUS
DOCUMENT NUMBER: 111:90155
TITLE: Influence of platelet factor 4 on the neutralization of heparin by **protamine**
AUTHOR(S): Shanberge, J. N.; Quattrociocchi-Longe, T. M.
CORPORATE SOURCE: Dep. Clin. Pathol., William Beaumont Hosp., Royal Oak, MI, 48072, USA
SOURCE: Annals of the New York Academy of Sciences (1989), 556(Heparin Relat. Polysaccharides), 354-65
CODEN: ANYAA9; ISSN: 0077-8923
DOCUMENT TYPE: Journal
LANGUAGE: English

L2 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
TI Heparin cofactor II assay. Elimination of heparin and antithrombin-III effects
AB Functional assays for heparin cofactor II (HC-II) are based on the inactivation of thrombin by HC-II in the presence of dermatan sulfate (DS). Residual thrombin is measured in a chromogenic assay. Interference by the antithrombin-III (AT-III)/heparin complex, which also rapidly inactivates thrombin, must be eliminated from the HC-II test system. Com. DS is contaminated with heparin, and plasma specimens to be tested contain AT-III. After $NaNO_2$/HOAc treatment of DS (to inactivate heparin), there was enough residual heparin to cause AT-III interference. Treatment of plasma with com. available anti-AT-III antiserum largely, but not completely, removed AT-III interference from the HC-II assay. With com. available reagents, both $NaNO_2$/acetic acid treatment of DS and anti-AT-III treatment of plasma were needed to eliminate heparin/AT-III interference. **Protamine** sulfate inactivated DS as well as heparin and could not be used to reduce AT-III/heparin interference with HC-II assay.

ACCESSION NUMBER: 1988:182553 HCAPLUS
DOCUMENT NUMBER: 108:182553
TITLE: Heparin cofactor II assay. Elimination of heparin and antithrombin-III effects
AUTHOR(S): Nakhleh, Raouf; Vogt, Janice M.; Edson, J. Roger
CORPORATE SOURCE: Sch. Med., Univ. Minnesota, Minneapolis, MN, USA
SOURCE: American Journal of Clinical Pathology (1988), 89(3), 353-8
CODEN: AJCPAI; ISSN: 0002-9173
DOCUMENT TYPE: Journal
LANGUAGE: English

L2 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
TI New antagonist of heparin: partially N-oxidized poly-allyldiethylamine
GI For diagram(s), see printed CA Issue.
AB Poly(allyldiethylamine N-oxide) (I) had marked antiheparin activity in vitro analogous to that of **protamine** sulfate, but the direct anticoagulant action of I was much less than that of **protamine**. The polymer with 80% of its tertiary amino groups N-oxidized had a lower anticoagulant action than the 70% N-oxidized polymer, probably due to the lower level of free amino groups present in the former mol.

ACCESSION NUMBER: 1971:11660 HCAPLUS
DOCUMENT NUMBER: 74:11660
TITLE: New antagonist of heparin: partially N-oxidized poly-allyldiethylamine
AUTHOR(S): Marchisio, Maria A.; Sbertoli, C.; Farina, G.; Ferruti, Paolo
CORPORATE SOURCE: Clin. Lavoro "L. Devoto", Univ. Milano, Milan, Italy
SOURCE: European Journal of Pharmacology (1970), 12(2), 236-42
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

L2 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
TI Hemostasis disturbance after extracorporeal circulation
AB An observed increase in the rate of thrombin formation and its subsequent degradation, in fibrinolytic activity, and heparin deactivation as well as the decrease in antithrombin III, thrombin time, and fibrinogen concentration were more pronounced in blood preserved in plastic than in siliconized glass containers, and in heparinized than in citrate-acid-dextrose treated blood. During perfusions lasting for more than 1 hr, especially after **protamine** addition, and **heparin inactivation**, disturbances in blood coagulation occur.
ACCESSION NUMBER: 1970:130113 HCAPLUS
DOCUMENT NUMBER: 72:130113
TITLE: Hemostasis disturbance after extracorporeal circulation
AUTHOR(S): Flesch, R.
CORPORATE SOURCE: Chir. Klin. Poliklin., Univ. Erlangen-Nuernberg, Erlangen, Fed. Rep. Ger.
SOURCE: Thoraxchirurgie, Vaskulaere Chirurgie (1969), 17(5), 422-6
CODEN: TVCHAF; ISSN: 0040-6384
DOCUMENT TYPE: Journal
LANGUAGE: German

L2 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
TI Effect of heparin on the inactivation of serum lipoprotein lipase by the liver in unanesthetized dogs
AB The efficiency of the liver in the inactivation of lipoprotein lipase (LPL) activity of serum obtained from a donor dog previously injected with heparin (20 units/kg.) was studied in intact unanesthetized dogs. The extraction ratio (portal vein-hepatic vein percentage difference) of LPL activity across the liver was 68% and 42% in 2 dogs. When LPL activity was generated by direct heparin injection into the exptl. animal, an extraction ratio of 40% was obtained. When 200 units heparin per kg. were injected, extraction ratios of only 10 and 4.7% were obtained. Following administration of **protamine** 15 min. after heparin injection, there was marked drop in the LPL activity of blood taken from the portal and hepatic veins and from the aorta. In a dog infused with heparin (20 units/kg.) LPL activity in serum drawn over the 1st 2-3 min. was 6.7 micromoles of free fatty acid per ml. serum/60 min. with no serum added to the assay system. There was a progressive decrease to 2.8 micromoles as the concentration of heparin was increased to 10 units/ml. LPL activity in serum drawn over the 9-10-min. interval decreased progressively from 2.4 to 1.5 micromoles as the concentration of heparin added to the assay system was increased to 10 units/ml. Stimulation of LPL activity with increasing heparin concentration was not observed in either the early or late serum samples. The results demonstrate the high efficiency of the hepatic LPL inactivation system in vivo. The results also indicate that high levels of heparin can block the latter system. A 2-step mechanism for hepatic LPL inactivation is suggested. Heparin first forms a complex with the LPL apoenzyme and enters the liver by the portal vein. The 1st inactivation step may

involve the destruction of heparin by a liver heparinase. This step may induce dissociation of the heparin-apoenzyme complex after which the apoenzyme is destroyed in a 2nd step.

ACCESSION NUMBER: 1969:469192 HCAPLUS
DOCUMENT NUMBER: 71:69192
TITLE: Effect of heparin on the inactivation of serum lipoprotein lipase by the liver in unanesthetized dogs
AUTHOR(S): Whayne, Thomas F., Jr.; Felts, James M.; Harris, Phillip A.
CORPORATE SOURCE: Med. Center, Univ. of California, San Francisco, CA, USA
SOURCE: Journal of Clinical Investigation (1969), 48(7), 1246-51
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

L2 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
TI **Protamine**, polybrene, and the antithrombin action of heparin
AB The antithrombin actions of heparin and normal plasma antithrombin are quite sep. effects. The antiheparins do not interfere with the progressive action of normal plasma antithrombin but neutralize the ability of heparin in conjunction with the plasma heparin cofactor to inactivate thrombin. **Protamine** and polybrene have the capacity to reverse the process of inactivation of thrombin by heparin and cofactor with the consequent release of thrombin activity. However, reversal does not follow the pattern of neutralization of heparin in that not all the inactivated thrombin is released by antiheparin at levels exceeding the neutralization point. The heparin cofactor complex provides an immediate and nonprogressive inactivation of thrombin and the action of heparin antagonists in reversing this effect produces an immediate and nonprogressive liberation of thrombin activity. Heparin and cofactor, therefore, merely inactivate thrombin without disposing of it. However, normal plasma antithrombin continues to degrade the thrombin held inactive by the complex so that the thrombin is eventually completely eliminated. Chromatographic evidence for the existence of a heparin-cofactor-thrombin complex was provided by gel filtration studies using Sephadex G-150. The implications of all these findings are discussed in relation to the function of heparinized intravascular prostheses.

ACCESSION NUMBER: 1968:67522 HCAPLUS
DOCUMENT NUMBER: 68:67522
TITLE: **Protamine**, polybrene, and the antithrombin action of heparin
AUTHOR(S): Porter, Philip; Porter, Margaret C.; Shanberge, Jacob N.
CORPORATE SOURCE: Evanston Hosp., Evanston, IL, USA
SOURCE: Clinica Chimica Acta (1968), 19(3), 411-20
CODEN: CCATAR; ISSN: 0009-8981
DOCUMENT TYPE: Journal
LANGUAGE: English

L2 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
TI The effect of heparin on the early stages of blood coagulation
AB Heparin combines with and inactivates Christmas factor by forming a reversible complex. Conversely, Christmas factor of plasma or serum, and especially the latter, platelet protein, and platelet-like activity of serum inactivate heparin. None of the other plasma or serum proteins act in this way. Prolongation of the clotting time of whole blood by addition of heparin appears to be due to the inactivation of Christmas factor by heparin. Some properties of the factor responsible for the platelet-like activity of serum, and its possible role in normal coagulation are discussed. The affinity of certain serum and plasma fractions for heparin was reported to be: β-lipoproteins < thrombin clotting system <

Christmas factor < platelet protein < **protamine** sulfate.

ACCESSION NUMBER: 1960:111099 HCAPLUS
DOCUMENT NUMBER: 54:111099
ORIGINAL REFERENCE NO.: 54:21266i,21267a-b
TITLE: The effect of heparin on the early stages of blood coagulation
AUTHOR(S): O'Brien, J. R.
CORPORATE SOURCE: Central Lab., Portsmouth, UK
SOURCE: Journal of Clinical Pathology (1960), 13, 93-8
CODEN: JCPAAK; ISSN: 0021-9746
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

L2 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
TI A heparin-inactivating material of the hypophysis front lobe
AB The antiheparin effect of a Cibacthen-NaCl solution is not changed after 1-hr. boiling in acid; its strength decreases at pH 7.3 to 11.0. Citrates or oxalated plasma as such or heated for 2 hrs. at 50° causes after several hrs. a decrease in antiheparin effect of Cibacthene, more so at 37° than at 5°. The physiol. NaCl extract of the hypophysis front lobe residue after adrenocorticotropin (ACTH) removal has the same characteristics as Cibacthen. The antiheparin substance contained in either can be dialyzed or ultrafiltered. They prevent metachromasia of toluidine blue solution to violet-red by heparin in quantities insufficient to show in clotting tests. The material is not of protein, **protamine**, or ACTH nature.

ACCESSION NUMBER: 1956:9336 HCAPLUS
DOCUMENT NUMBER: 50:9336
ORIGINAL REFERENCE NO.: 50:2006f-h
TITLE: A heparin-inactivating material of the hypophysis front lobe
AUTHOR(S): Kohler, Valentin
CORPORATE SOURCE: Univ. Wurzburg, Germany
SOURCE: Naturwissenschaften (1955), 42, 99
CODEN: NATWAY; ISSN: 0028-1042
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

L2 ANSWER 16 OF 16 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI AMINO ACID COMPOSITION HETEROGENEITY AND ANTIHEPARIN ACTIVITY OF **PROTAMINE** SULFATE FROM STURGEON MILT ROE ACIPENSER-STURIO.
AB The homogeneous preparation of **protamine** sulphate is obtained chromatographically and electrophoretically from milt roe of the sturgeon. Its amino acid composition and properties are studied. The methods of blockade the functional groups of **protamine** sulphate amino acids is used to investigate the possible mechanism of **heparin inactivation**.

ACCESSION NUMBER: 1990:136075 BIOSIS
DOCUMENT NUMBER: PREV199089074886; BA89:74886
TITLE: AMINO ACID COMPOSITION HETEROGENEITY AND ANTIHEPARIN ACTIVITY OF **PROTAMINE** SULFATE FROM STURGEON MILT ROE ACIPENSER-STURIO.
AUTHOR(S): BORODINSKAYA I N [Reprint author]; MISHUNIN I F
CORPORATE SOURCE: AV PALLADIN INST BIOCHEM, ACAD SCI UKR SSR, KIEV, USSR
SOURCE: Ukrainskii Biokhimicheskii Zhurnal, (1989) Vol. 61, No. 6, pp. 84-88.
CODEN: UBZHD4. ISSN: 0201-8470.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: RUSSIAN
ENTRY DATE: Entered STN: 13 Mar 1990
Last Updated on STN: 13 Mar 1990

```
=> s low moleculare weight protamine
L3            0 LOW MOLECULARE WEIGHT PROTAMINE

=> s (low moleculare weight protamine)
L4            0 (LOW MOLECULARE WEIGHT PROTAMINE)

=> s low molecular weight protamine
L5           51 LOW MOLECULAR WEIGHT PROTAMINE

=> s protamine and Low molecular weight
L6         2344 PROTAMINE AND LOW MOLECULAR WEIGHT

=> s l6 and l5
L7           51 L6 AND L5

=> s l7 and (heparin inactivation)
L8            0 L7 AND (HEPARIN INACTIVATION)

=> s l7 and (heparin)
L9           34 L7 AND (HEPARIN)

=> d l9 ti abs ibib tot

L9   ANSWER 1 OF 34     MEDLINE on STN
TI   The minimal functional sequence of protamine.
AB   Despite its nearly universal applications, protamine, a mixture
     of four major peptides with different sequences, is associated with
     clinically significant side effects. Through a well-designed enzyme
     digestion method, various low molecular weight
     protamine peptides were obtained. Among them, two low
     molecular weight protamine peptides with the
     same or even more potent heparin neutralization abilities as
     native protamine were identified through both in vitro and in
     vivo tests. In addition, in vivo experiments showed that compared to
     native protamine, these two low molecular
     weight protamine peptides were less toxic and would be
     safer for clinical use.
ACCESSION NUMBER:    2005493644     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 16139792
TITLE:               The minimal functional sequence of protamine.
AUTHOR:              Liang Jun Feng; Yang Victor C; Vaynshteyn Yekaterina
CORPORATE SOURCE:    Department of Chemistry and Chemical Biology, Stevens
                     Institute of Technology, Hoboken, NJ 07030, USA.
CONTRACT NUMBER:     CA114612 (NCI)
SOURCE:              Biochemical and biophysical research communications, (2005
                     Oct 21) Vol. 336, No. 2, pp. 653-9.
                     Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200511
ENTRY DATE:          Entered STN: 17 Sep 2005
                     Last Updated on STN: 16 Nov 2005
                     Entered Medline: 15 Nov 2005

L9   ANSWER 2 OF 34     MEDLINE on STN
TI   A less toxic heparin antagonist--low molecular
     weight protamine.
AB   A new thirteen amino acid peptide, named low molecular
     weight protamine (LMWP), was obtained through the
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enzymatic digestion of native **protamine**. Both in vitro and in vivo results showed that LMWP fully maintained the **heparin** neutralization function of **protamine** but had much lower immunogenicity and antigenicity. Unlike **protamine**, neither LMWP nor LMWP/**heparin** complexes caused significant blood platelet aggregation in rats. These results suggest that LMWP can be used as a substitute for **protamine** for developing a new generation of nontoxic **heparin** antagonists.

ACCESSION NUMBER: 2003176203 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12693985
TITLE: A less toxic **heparin** antagonist--**low molecular weight protamine**.
AUTHOR: Liang J F; Zhen L; Chang L-C; Yang V C
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109-1065, USA.. junfeng@umich.edu
SOURCE: Biochemistry. Biokhimii a, (2003 Jan) Vol. 68, No. 1, pp. 116-20.
Journal code: 0376536. ISSN: 0006-2979.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 17 Apr 2003
Last Updated on STN: 17 Dec 2003
Entered Medline: 5 Dec 2003

L9 ANSWER 3 OF 34 MEDLINE on STN
TI **Low molecular weight protamine** as nontoxic **heparin/low molecular weight heparin** antidote (III): preliminary in vivo evaluation of efficacy and toxicity using a canine model.
AB **Heparin** employed in cardiovascular surgeries often leads to a high incidence of bleeding complications. **Protamine** employed in **heparin** reversal, however, can cause severe adverse reactions. In an attempt to address this clinical problem, we developed **low molecular weight protamine** (LMWP) as a potentially effective and less toxic **heparin** antagonist. A homogeneous 1880-d peptide fragment, termed LMWP-TDSP5 and containing the amino acid sequence of VSRRRRRRGGRRRR, was derived directly from **protamine** by enzymatic digestion of **protamine** with thermolysin. In vitro studies demonstrated that TDSP5 was capable of neutralizing various anticoagulant functions of both **heparin** and commercial **low molecular weight heparin** preparations. In addition, TDSP5 exhibited significantly reduced crossreactivity toward mouse sera containing antiprotamine antibodies. TDSP5 showed a decrease in its potential in activating the complement system. All of these findings suggested the possibility of markedly reduced **protamine** toxicity for TDSP5. In this article, we conducted preliminary in vivo studies to further demonstrate the feasibility and utility of using LMWP as a nontoxic clinical **protamine** substitute. Dogs were chosen as test animals because they were known to magnify the typical human response to **protamine**. By using a full spectra of biological and clinical assays for **heparin**, including the anti-IIa and anti-Xa chromogenic assays and the activated partial, thromboplastin time and TCT clotting assays, TDSP5 showed that it could completely neutralize all these different anticoagulant functions of **heparin** in dogs. Although administration of **protamine** in dogs produced a significant reduction in mean arterial blood pressure (-14.9 mm Hg) and elevation in pulmonary artery systolic pressure (+5.0 mm Hg), the use of TDSP5 in dogs did not elicit any statistically significant change in any of the variables measured. Furthermore, the use of LMWP also significantly

reduced the **protamine**-induced transient thrombocytopenic and granulocytopenic responses. The white blood cell counts and platelet counts decreased to 82.1% and 60.0% of baseline, respectively, in dogs given intravenous **protamine** compared to 97.8% and 88.6% of baseline in dogs receiving TDSP5. These preliminary findings indicated that LMWP could potentially provide an effective and safe means to control both **heparin**- and **protamine**-induced complications.

ACCESSION NUMBER: 2001700733 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11741270
TITLE: **Low molecular weight protamine** as nontoxic **heparin/low molecular weight heparin** antidote (III): preliminary in vivo evaluation of efficacy and toxicity using a canine model.
AUTHOR: Lee L M; Chang L C; Wrobleski S; Wakefield T W; Yang V C
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109, USA.
CONTRACT NUMBER: HL38353 (NHLBI)
SOURCE: AAPS pharmSci [electronic resource], (2001) Vol. 3, No. 3, pp. E19.
Journal code: 100897065. E-ISSN: 1522-1059.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20 Dec 2001
Last Updated on STN: 22 Feb 2002
Entered Medline: 21 Feb 2002

L9 ANSWER 4 OF 34 MEDLINE on STN
TI **Low molecular weight protamine** (LMWP) as nontoxic **heparin/low molecular weight heparin** antidote (II): in vitro evaluation of efficacy and toxicity.
AB Patients undergoing anticoagulation with **heparin** or **low molecular weight heparin** (LMWH) require a superior antidote that possesses more selective biological actions and a better safety profile than **protamine**. We had previously developed 2 **low molecular weight protamine** (LMWP) fractions (TDSP4 and TDSP5) from thermolysin-digested **protamine** as potential nontoxic, **heparin**-neutralizing agents. In this, the second article in this series, studies focused on in vitro evaluation of **heparin** /LMWH-neutralizing efficacy and putative toxicity. These LMWP fractions, particularly TDSP5, were effective and fully capable of neutralizing a broad spectrum of **heparin**-induced anticoagulant activities (ie, aPTT, anti-Xa, and anti-IIa activities). Additionally, these LMWP fractions could neutralize the activities of commercial LMWH. As assessed by the anti-Xa assay, TDSP5 was as effective as, although less potent than, **protamine** in reversing the activity of Mono-Embolex (molecular weight 5000-7000) and 2 other different sizes (molecular weight of 3000 and 5000 d) of LMWH preparations. Furthermore, compared with **protamine**, TDSP5 exhibited a much-reduced toxicity and thus an improved safety profile, as reflected by its reduced ability to activate the complement system and cross-react with the antiprotamine antibodies, which are 2 primary indices of **protamine** toxicity.

ACCESSION NUMBER: 2001700732 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11741269
TITLE: **Low molecular weight protamine** (LMWP) as nontoxic **heparin/low molecular weight heparin** antidote (II): in vitro evaluation of

efficacy and toxicity.
AUTHOR: Chang L C; Liang J F; Lee H F; Lee L M; Yang V C
CORPORATE SOURCE: School of Pharmacy, National Defense Medical Center, Taipei, Taiwan.
CONTRACT NUMBER: HL38353 (NHLBI)
SOURCE: AAPS pharmSci [electronic resource], (2001) Vol. 3, No. 3, pp. E18.
Journal code: 100897065. E-ISSN: 1522-1059.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20 Dec 2001
Last Updated on STN: 22 Feb 2002
Entered Medline: 21 Feb 2002

L9 ANSWER 5 OF 34 MEDLINE on STN
TI **Low molecular weight protamine** (LMWP) as nontoxic **heparin/low molecular weight heparin** antidote (I): preparation and characterization.
AB **Low molecular weight protamine** (LMWP) appears to be a promising solution for **heparin** neutralization without the **protamine**-associated catastrophic toxic effects. The feasibility of this hypothesis was proven previously by using a peptide mixture produced from proteolytic digestion of **protamine**. To further examine the utility of this compound as an ultimate nontoxic **protamine** substitute, detailed studies on the purification and characterization of LMWP including the precise amino acid sequence, structure-function relationship, and possible mechanism were conducted. A number of LWMP fragments, composed of highly cationic peptides with molecular weights ranging from 700 to 1900 d, were prepared by digestion of native **protamine** with the protease thermolysin. These fragments were fractionated using a **heparin** affinity chromatography, and their relative binding strengths toward **heparin** were elucidated. Five distinct fractions were eluted at NaCl concentration ranging from 0.4 to 1.0 M and were denoted as TDSP1 to TDSP5, in increasing order of eluting ionic strength. Among these 5 fractions, TDSP4 and TDSP5 contained 3 LMWP peptide fragments, and they were found to retain the complete **heparin**-neutralizing function of **protamine**. By using a peptide mass spectrometry (MS) fingerprint mapping technique, the amino acid sequences of the microheterogeneous LMWP fragments in all these 5 elution fractions were readily identified. A typical structural scaffold made by arginine clusters in the middle and nonarginine residues at the N-terminal of the peptide sequence was observed for all these LMWP fragments. By aligning the sequences with the potency in **heparin** neutralization of these LMWP fragments, it was found that retention of potency similar to that of **protamine** required the presence of at least 2 arginine clusters in the LMWP fragments; such as the sequence of VSRRRRRRGGRRRR seen in the most potent LMWP fraction-TDSP5. The above finding was further validated by using a synthetic LMWP analogue-CRRRRRRR-and it was found that its **heparin**-neutralizing ability was increased by changing from a monomeric to a dimeric structure of this analogue peptide. Based on these results, the structural requirement for a compound to function as an effective **heparin** antidote and the possible mechanism involved in **heparin** neutralization were established.
ACCESSION NUMBER: 2001700731 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11741268
TITLE: **Low molecular weight protamine** (LMWP) as nontoxic **heparin/low molecular weight**

**heparin** antidote (I): preparation and characterization.
AUTHOR: Chang L C; Lee H F; Yang Z; Yang V C
CORPORATE SOURCE: School of Pharmacy, National Defense Medical Center, Taipei, Taiwan.
CONTRACT NUMBER: HL38353 (NHLBI)
SOURCE: AAPS pharmSci [electronic resource], (2001) Vol. 3, No. 3, pp. E17.
Journal code: 100897065. E-ISSN: 1522-1059.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20 Dec 2001
Last Updated on STN: 22 Feb 2002
Entered Medline: 21 Feb 2002

L9 ANSWER 6 OF 34 MEDLINE on STN
TI **Low molecular weight protamine**: a potent but nontoxic antagonist to **heparin/low molecular weight protamine**.
AB To avoid bleeding complications, **protamine** is routinely used after cardiovascular surgery to neutralize the anticoagulant function of **heparin**. However, its clinical use is associated with adverse and sometimes fatal reactions. Based on literature review of the mechanism of **heparin** neutralization and **protamine** induced immunologic toxicity, we propose the following hypothesis: If a chain shortened **low molecular weight protamine** (LMWP) containing the **heparin** neutralizing domain could be derived from native **protamine**, it could be a potent and yet nontoxic **heparin** antagonist. In this study, we present results to validate this hypothesis. LMWP fragments containing an intact arginine sequence and an average molecular weight of approximately 1,100 daltons were successfully prepared by enzymatic digestion of **protamine** with thermolysin. In vitro studies show that such LMWP fragments completely neutralized the anticoagulant functions of **heparin** and LMWH, based on the anti-Xa chromogenic and aPTT clotting time assays. In vivo results reveal that although injection of **protamine** to mice led to obvious production of anti-**protamine** antibodies, injection of LMWP did not elicit any detectable immunogenic responses. In addition, these LMWP fragments exhibited a markedly reduced antigenicity and cross-reactivity toward the mice anti-**protamine** antibodies.
ACCESSION NUMBER: 2001036337 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10926141
TITLE: **Low molecular weight protamine**: a potent but nontoxic antagonist to **heparin/low molecular weight protamine**.
AUTHOR: Byun Y; Chang L C; Lee L M; Han I S; Singh V K; Yang V C
CORPORATE SOURCE: College of Pharmacy, University of Michigan, Ann Arbor 48109-1065, USA.
CONTRACT NUMBER: HL38353 (NHLBI)
HL55461 (NHLBI)
SOURCE: ASAIO journal (American Society for Artificial Internal Organs : 1992), (2000 Jul-Aug) Vol. 46, No. 4, pp. 435-9.
Journal code: 9204109. ISSN: 1058-2916.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 22 Mar 2001

Last Updated on STN: 22 Mar 2001
Entered Medline: 28 Nov 2000

L9 ANSWER 7 OF 34 MEDLINE on STN
TI **Low molecular weight protamine**: a potential nontoxic **heparin** antagonist.
AB **Protamine** sulfate is the universal clinical antagonist to **heparin** and is used routinely after cardiovascular surgery to neutralize the anticoagulant function of **heparin**. Its clinical use, however, is associated with adverse effects including idiosyncratic fatal reactions. An examination of the mechanism of **heparin** neutralization and **protamine** toxicity suggests that the reversal of **heparin** anticoagulation may only require a small arginine-rich fragment of **protamine** to electrostatically dissociate antithrombin III from its binding to a specific pentasaccharide sequence in **heparin**. A review of literature indicates that chain-shortened peptide fragments derived from their parent proteins are normally accompanied with significantly reduced antigenicity and immunogenicity, which are two primary contributing factors to **protamine**-induced life-threatening toxic effects via an immunoglobulin-mediated pathway. Based on these observations, we propose our general hypothesis: if a chain-shortened **low molecular weight protamine** fragment containing the **heparin**-neutralizing domain could be derived directly from a native **protamine**, it could be a potent and nontoxic **heparin** antagonist. In this article, we present our experimental results to support the above hypothesis. LMWP fragments containing an intact arginine sequence and an average molecular weight of approximately 1.1 kDa were prepared successfully by enzymatic digestion of native **protamine** with thermolysin. In vitro studies demonstrated that such LMWP fragments completely neutralized the anticoagulant functions of **heparin**, based on the anti-Xa chromogenic assay and aPTT clotting time assay. Our in vivo results indicated that while administration of **protamine** to mice led to obvious production of antiprotamine antibodies, injection of LMWP did not elicit any detectable immunogenic responses. In addition, the LMWP fragments showed a significantly reduced antigenicity or, in other words, cross-reactivity towards the mice antiprotamine antibodies produced by the administration of **protamine**.
ACCESSION NUMBER: 1999228169 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10213181
TITLE: **Low molecular weight protamine**: a potential nontoxic **heparin** antagonist.
AUTHOR: Byun Y; Singh V K; Yang V C
CORPORATE SOURCE: Department of Pharmaceutics, College of Pharmacy, The University of Michigan, Ann Arbor 48105-1069, USA.
CONTRACT NUMBER: HL38353 (NHLBI)
HL55461 (NHLBI)
SOURCE: Thrombosis research, (1999 Apr 1) Vol. 94, No. 1, pp. 53-61.
Journal code: 0326377. ISSN: 0049-3848.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 25 May 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 13 May 1999

L9 ANSWER 8 OF 34 USPATFULL on STN
TI Immunogenic composition and method of developing a vaccine based on

fusion protein

AB The present invention relates to an immunogenic composition. More particularly, the present invention is a composition directed to eliciting an immune response to HIV fusion protein. The present invention contemplates three categories of embodiments: protein or protein fragments, messenger RNA, or DNA/RNA. DNA/RNA compositions may be either naked or recombinant. The present invention further contemplates use with a variety of immune stimulants.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | | | |
|---|---|---|---|
| ACCESSION NUMBER: | 2005:247123 USPATFULL | | |
| TITLE: | Immunogenic composition and method of developing a vaccine based on fusion protein | | |
| INVENTOR(S): | Karp, Nelson M., Virginia Beach, VA, UNITED STATES | | |
| PATENT ASSIGNEE(S): | NMK Research, LLC (U.S. corporation) | | |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2005214318 | A1 | 20050929 | |
| APPLICATION INFO.: | US 2004-971426 | A1 | 20041022 | (10) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2003-513827P | 20031023 (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | APPLICATION |
| LEGAL REPRESENTATIVE: | ART & ALICE DUECK, BOX 98, ROSTHERN, SK, S0K 3R0, CA |
| NUMBER OF CLAIMS: | 31 |
| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 8 Drawing Page(s) |
| LINE COUNT: | 2127 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 9 OF 34 USPATFULL on STN

TI Immunogenic composition and method of developing a vaccine based on cyclophilin a binding site

AB The present invention relates to an immunogenic composition. More particularly, the present invention is a composition directed to eliciting an immune response to at least one binding site of Cyclophilin A on the HIV capsid protein. (SEQ ID NOS: 2, 4, and 6) The present invention contemplates three categories of embodiments: protein or protein fragments (SEQ ID NOS: 2, 4, and 6), messenger RNA, or DNA/RNA. DNA/RNA compositions (SEQ ID NOS 1, 3, 5, 7, 9, and 11) may be either naked or recombinant. The present invention further contemplates use with a variety of immune stimulants.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | | | |
|---|---|---|---|
| ACCESSION NUMBER: | 2005:247122 USPATFULL | | |
| TITLE: | Immunogenic composition and method of developing a vaccine based on cyclophilin a binding site | | |
| INVENTOR(S): | Karp, Nelson M., Virginia Beach, VA, UNITED STATES | | |
| PATENT ASSIGNEE(S): | NMK Research, LLC (U.S. corporation) | | |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2005214317 | A1 | 20050929 | |
| APPLICATION INFO.: | US 2004-971199 | A1 | 20041022 | (10) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2003-513827P | 20031023 (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | APPLICATION |

LEGAL REPRESENTATIVE: M. Bruce Harper, 222 Central Park Ave., Suite 1700, Virginia Beach, VA, 23462-3035, US
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 2324
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 10 OF 34 USPATFULL on STN
TI Polysaccharides for pulmonary delivery of active agents
AB Formulation for pulmonary delivery of a therapeutic, prophylactic, or diagnostic agent including a **low molecular weight heparin** and a therapeutic, prophylactic, or diagnostic agent.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2005:239988 USPATFULL
TITLE: Polysaccharides for pulmonary delivery of active agents
INVENTOR(S): Richardson, Thomas, South Boston, MA, UNITED STATES
Venkataraman, Ganesh, Bedford, MA, UNITED STATES
Qi, Yiwei, Andover, MA, UNITED STATES
Picard, Michele, Dover, MA, UNITED STATES

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2005207988 | A1 | 20050922 | |
| APPLICATION INFO.: | US 2004-957218 | A1 | 20041001 | (10) |

| | NUMBER | DATE | |
|---|---|---|---|
| PRIORITY INFORMATION: | US 2004-580869P | 20040618 | (60) |
| | US 2003-508062P | 20031001 | (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & RICHARDSON PC, P.O. BOX 1022, MINNEAPOLIS, MN, 55440-1022, US
NUMBER OF CLAIMS: 82
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 3145
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 11 OF 34 USPATFULL on STN
TI Method of developing an immunogenic composition and HIV vaccine
AB An antigenic and immunogenic composition of predetermined inactivated strains of human immunodeficiency virus (HIV) is disclosed. Inactivation is through psoralen and ultraviolet radiation; the composition is rendered more effective by the removal of structural features of HIV that interfere with immune response. In particular, sialic acid is removed to enhance immune recognition of the composition and to impair Complement Factor H binding. CD55 and CD59 are also removed to prevent the binding of Complement Factor H. Determination of strains for inactivation may be though immunotherapeutic genotyping or probabilistic assessment of risk of exposure.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2005:130684 USPATFULL
TITLE: Method of developing an immunogenic composition and HIV vaccine
INVENTOR(S): Karp, Nelson M., Virginia Beach, VA, UNITED STATES
PATENT ASSIGNEE(S): NMK Research, LLC (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|

| | | | |
|---|---|---|---|
| PATENT INFORMATION: | US 2005112143 | A1 | 20050526 |
| APPLICATION INFO.: | US 2004-971445 | A1 | 20041022 (10) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2003-513827P | 20031023 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: M. Bruce Harper, Suite 1700, 222 Central Park Ave., Virginia Beach, VA, 23462-3035, US
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 1253
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 12 OF 34 USPATFULL on STN
TI Immunogenic composition and method of developing a vaccine based on portions of the HIV matrix protein
AB The present invention relates to an immunogenic composition. More particularly, the present invention is a composition directed to eliciting an immune response to at least one covalent binding site of myristate on the HIV matrix protein. The present invention contemplates three categories of embodiments: protein or protein fragments, messenger RNA, or DNA/RNA. DNA/RNA compositions may be either naked or recombinant. The present invention further contemplates use with a variety of immune stimulants.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2005:130681 USPATFULL
TITLE: Immunogenic composition and method of developing a vaccine based on portions of the HIV matrix protein
INVENTOR(S): Karp, Nelson M., Virginia Beach, VA, UNITED STATES
PATENT ASSIGNEE(S): NMK Research, LLC (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2005112140 | A1 | 20050526 |
| APPLICATION INFO.: | US 2004-971229 | A1 | 20041022 (10) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2003-513827P | 20031023 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ART & ALICE DUECK, BOX 98, ROSTHERN, SK, S0K 3R0, CA
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 2257
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 13 OF 34 USPATFULL on STN
TI Immunogenic composition and method of developing a vaccine based on factor H binding sites
AB An immunogenic composition able to provide an immune response to Human Complement Factor H binding on one or more HIV glycoproteins is disclosed, which is characterized by at least one binding site epitope of the glycoproteins. Such immunogenic composition wherein the glycoprotein comprises gp120, gp41, or both glycoproteins gp120 and gp41 is hereby disclosed. Sialic acid is removed to enhance immune recognition of the composition and to impair Factor H binding. A

medication having an inhibitive action on autoimmune response by specific inhibition of the cleavage of C3b by Factor H into inactive cell fragments.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | |
|---|---|
| ACCESSION NUMBER: | 2005:130680 USPATFULL |
| TITLE: | Immunogenic composition and method of developing a vaccine based on factor H binding sites |
| INVENTOR(S): | Karp, Nelson M., Virginia Beach, VA, UNITED STATES |
| PATENT ASSIGNEE(S): | NMK Research, LLC (U.S. corporation) |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2005112139 | A1 | 20050526 |
| APPLICATION INFO.: | US 2004-971219 | A1 | 20041022 (10) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2003-513827P | 20031023 (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | APPLICATION |
| LEGAL REPRESENTATIVE: | WILLIAMS MULLEN, 222 CENTRAL PARK AVENUE, SUITE 1700, VIRGINIA BEACH, VA, 23462-3035, US |
| NUMBER OF CLAIMS: | 34 |
| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 13 Drawing Page(s) |
| LINE COUNT: | 2357 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 14 OF 34 USPATFULL on STN

TI **Protamine** fragment compositions and methods of use

AB Provided are bioactive, low-toxicity **protamine** fragments, compositions, combinations, kits and methods of using these components in a variety of embodiments, including neutralizing **heparin** and reducing post-operative bleeding. Improved **protamine** fragment-insulin solutions and methods for treating diabetes are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | |
|---|---|
| ACCESSION NUMBER: | 2005:118259 USPATFULL |
| TITLE: | **Protamine** fragment compositions and methods of use |
| INVENTOR(S): | Yang, Victor C., Ann Arbor, MI, UNITED STATES<br>Byun, Youngro, Kwangsan-Ku Kwangju, KOREA, REPUBLIC OF |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2005101532 | A1 | 20050512 |
| APPLICATION INFO.: | US 2003-668663 | A1 | 20030923 (10) |
| RELATED APPLN. INFO.: | Division of Ser. No. US 2000-700967, filed on 16 Nov 2000, GRANTED, Pat. No. US 6624141 A 371 of International Ser. No. WO 2000-US6876, filed on 15 Mar 2000 | | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1999-124873P | 19990317 (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | APPLICATION |
| LEGAL REPRESENTATIVE: | WILLIAMS, MORGAN & AMERSON, P.C., 10333 RICHMOND, SUITE 1100, HOUSTON, TX, 77042, US |
| NUMBER OF CLAIMS: | 19 |
| EXEMPLARY CLAIM: | 1-47 |

NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 2727
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 15 OF 34 USPATFULL on STN
TI Drug delivery compositions
AB The present invention relates to multicomponent compositions and methods of administering these compositions, which specifically translocate therapeutic molecules (e.g., drugs or prodrugs) across biological membranes thus reducing potential toxic side effects on nontargeted cells and tissues.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | | | |
|---|---|---|---|
| ACCESSION NUMBER: | 2005:49957 USPATFULL | | |
| TITLE: | Drug delivery compositions | | |
| INVENTOR(S): | Yang, Victor C., Ann Arbor, MI, UNITED STATES<br>Park, Yoon Jeong, Seoul, KOREA, REPUBLIC OF<br>Liang, Junfeng, Westfield, NJ, UNITED STATES | | |
| PATENT ASSIGNEE(S): | The Regents of the University of Michigan, Ann Arbor, MI (U.S. corporation) | | |
| | NUMBER | KIND | DATE |
| PATENT INFORMATION: | US 2005042753 | A1 | 20050224 |
| APPLICATION INFO.: | US 2004-835151 | A1 | 20040429 (10) |
| | NUMBER | | DATE |
| PRIORITY INFORMATION: | US 2003-466804P | | 20030430 (60) |
| | US 2003-466811P | | 20030430 (60) |
| DOCUMENT TYPE: | Utility | | |
| FILE SEGMENT: | APPLICATION | | |
| LEGAL REPRESENTATIVE: | Jason R. Bond, MEDLEN & CARROLL, LLP, Suite 350, 101 Howard Street, San Francisco, CA, 94105 | | |
| NUMBER OF CLAIMS: | 19 | | |
| EXEMPLARY CLAIM: | 1 | | |
| NUMBER OF DRAWINGS: | 24 Drawing Page(s) | | |
| LINE COUNT: | 6611 | | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 16 OF 34 USPATFULL on STN
TI Methods and products for mucosal delivery
AB The invention features methods and products associated with non-invasive delivery of polysaccharide preparations.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | | | |
|---|---|---|---|
| ACCESSION NUMBER: | 2004:114697 USPATFULL | | |
| TITLE: | Methods and products for mucosal delivery | | |
| INVENTOR(S): | Shriver, Zachary, Boston, MA, UNITED STATES<br>Venkataraman, Ganesh, Bedford, MA, UNITED STATES<br>Sundaram, Mallikarjun, Ashland, MA, UNITED STATES<br>Sasisekharan, Ram, Cambridge, MA, UNITED STATES<br>Richardson, Thomas, South Boston, MA, UNITED STATES<br>Qi, Yiwei, Charlestown, MA, UNITED STATES | | |
| | NUMBER | KIND | DATE |
| PATENT INFORMATION: | US 2004087543 | A1 | 20040506 |
| APPLICATION INFO.: | US 2003-423725 | A1 | 20030425 (10) |
| | NUMBER | | DATE |
| PRIORITY INFORMATION: | US 2002-375927P | | 20020425 (60) |

| | | |
|---|---|---|
| | US 2002-375970P | 20020425 (60) |
| | US 2002-383926P | 20020528 (60) |
| | US 2002-393959P | 20020705 (60) |
| | US 2003-446432P | 20030210 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110
NUMBER OF CLAIMS: 234
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 4010
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 17 OF 34 USPATFULL on STN
TI **Protamine** fragment compositions and methods of use
AB Provided are bioactive, low-toxicity **protamine** fragments, compositions, combinations, kits and methods of using these components in a variety of embodiments, including neutralizing **heparin** and reducing post-operative bleeding. Improved **protamine** fragment-insulin solutions and methods for treating diabetes are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:253624 USPATFULL
TITLE: **Protamine** fragment compositions and methods of use
INVENTOR(S): Yang, Victor C., Ann Arbor, MI, United States
Byun, Youngro, Kwangsan-Ku Kwangju, KOREA, REPUBLIC OF
PATENT ASSIGNEE(S): The Regents of The University of Michigan, Ann Arbor, MI, United States (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 6624141 | B1 | 20030923 | |
| | WO 2000055196 | | 20000921 | |
| APPLICATION INFO.: | US 2000-700967 | | 20001116 | (9) |
| | WO 1999-US6876 | | 19990309 | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1999-124873P | 19990317 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Low, Christopher S. F.
ASSISTANT EXAMINER: Robinson, Hope A.
LEGAL REPRESENTATIVE: Williams, Morgan and Amerson
NUMBER OF CLAIMS: 89
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 2952
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 18 OF 34 EMBASE 
TI The minimal functional sequence of **protamine**.
AB Despite its nearly universal applications, **protamine**, a mixture of four major peptides with different sequences, is associated with clinically significant side effects. Through a well-designed enzyme digestion method, various **low molecular weight protamine** peptides were obtained. Among them, two **low molecular weight protamine** peptides with the same or even more potent **heparin** neutralization abilities as

native **protamine** were identified through both in vitro and in vivo tests. In addition, in vivo experiments showed that compared to native **protamine**, these two **low molecular weight protamine** peptides were less toxic and would be safer for clinical use. .COPYRGT. 2005 Elsevier Inc. All rights reserved.

ACCESSION NUMBER: 2005407564 EMBASE
TITLE: The minimal functional sequence of **protamine**.
AUTHOR: Liang J.F.; Yang V.C.; Vaynshteyn Y.
CORPORATE SOURCE: J.F. Liang, Department of Chemistry and Chemical Biology, Stevens Institute of Technology, Hoboken, NJ 07030, United States
SOURCE: Biochemical and Biophysical Research Communications, (21 Oct 2005) Vol. 336, No. 2, pp. 653-659. .
Refs: 26
ISSN: 0006-291X CODEN: BBRCA
PUBLISHER IDENT.: S 0006-291X(05)01692-X
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Sep 2005
Last Updated on STN: 29 Sep 2005

L9 ANSWER 19 OF 34 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

TI **Low molecular weight protamine**: A potent but nontoxic antagonist to **heparin/low molecular weight protamine**.

AB To avoid bleeding complications, **protamine** is routinely used after cardiovascular surgery to neutralize the anticoagulant function of **heparin**. However, its clinical use is associated with adverse and sometimes fatal reactions. Based on literature review of the mechanism of **heparin** neutralization and **protamine** induced immunologic toxicity, we propose the following hypothesis: If a chain shortened **low molecular weight protamine** (LMWP) containing the **heparin** neutralizing domain could be derived from native **protamine**, it could be a potent and yet nontoxic **heparin** antagonist. In this study, we present results to validate this hypothesis. LMWP fragments containing an intact arginine sequence and an average molecular weigh of approximately 1,100 daltons were successfully prepared by enzymatic digestion of **protamine** with thermolysin. In vitro studies show that such LMWP fragments completely neutralized the anticoagulant functions of **heparin** and LMWH, based on the anti-Xa chromogenic and aPTT clotting time assays. In vivo results reveal that although injection of **protamine** to mice led to obvious production of anti-**protamine** antibodies, injection of LMWP did not elicit any detectable immunogenic responses. In addition, these LMWP fragments exhibited a markedly reduced antigenicity and cross-reactivity toward the mice anti-**protamine** antibodies.

ACCESSION NUMBER: 2000252410 EMBASE
TITLE: **Low molecular weight protamine**: A potent but nontoxic antagonist to **heparin/low molecular weight protamine**.
AUTHOR: Byun Y.; Chang L.-C.; Lee L.-M.; In Suk Han; Singh V.K.; Yang V.C.
CORPORATE SOURCE: Dr. V.C. Yang, College of Pharmacy, University of Michigan, 428 Church Street, Ann Arbor, MI 48109-1065, United States
SOURCE: ASAIO Journal, (2000) Vol. 46, No. 4, pp. 435-439. .
Refs: 19

ISSN: 1058-2916 CODEN: AJOUET
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 009 Surgery
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Aug 2000
Last Updated on STN: 3 Aug 2000

L9 ANSWER 20 OF 34 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

TI **Low molecular weight protamine**: A potential nontoxic **heparin** antagonist.

AB **Protamine** sulfate is the universal clinical antagonist to **heparin** and is used routinely after cardiovascular surgery to neutralize the anticoagulant function of **heparin**. Its clinical use, however, is associated with adverse effects including idiosyncratic fatal reactions. An examination of the mechanism of **heparin** neutralization and **protamine** toxicity suggests that the reversal of **heparin** anticoagulation may only require a small arginine-rich fragment of **protamine** to electrostatically dissociate antithrombin III from its binding to a specific pentasaccharide sequence in **heparin**. A review of literature indicates that chain-shortened peptide fragments derived from their parent proteins are normally accompanied with significantly reduced antigenicity and immunogenicity, which are two primary contributing factors to **protamine**-induced life-threatening toxic effects via an immunoglobulin- mediated pathway. Based on these observations, we propose our general hypothesis: if a chain-shortened **low molecular weight protamine** fragment containing the **heparin**-neutralizing domain could be derived directly from a native **protamine**, it could be a potent and nontoxic **heparin** antagonist. In this article, we present our experimental results to support the above hypothesis. LMWP fragments containing an intact arginine sequence and an average molecular weigh of approximately 1.1 kDa were prepared successfully by enzymatic digestion of native **protamine** with thermolysin. In vitro studies demonstrated that such LMWP fragments completely neutralized the anticoagulant functions of **heparin**, based on the anti-Xa chromogenic assay and aPTT clotting time assay. Our in vivo results indicated that while administration of **protamine** to mice led to obvious production of antiprotamine antibodies, injection of LMWP did not elicit any detectable immunogenic responses. In addition, the LMWP fragments showed a significantly reduced antigenicity or, in other words, cross-reactivity towards the mice antiprotamine antibodies produced by the administration of **protamine**.

ACCESSION NUMBER: 1999130746 EMBASE
TITLE: **Low molecular weight protamine**: A potential nontoxic **heparin** antagonist.
AUTHOR: Byun Y.; Singh V.K.; Yang V.C.
CORPORATE SOURCE: V.C. Yang, College of Pharmacy, University of Michigan, 428 Church Street, Ann Arbor, MI 48105-1069, United States. vcyang@umich.edu
SOURCE: Thrombosis Research, (1 Apr 1999) Vol. 94, No. 1, pp. 53-61. .
Refs: 27
ISSN: 0049-3848 CODEN: THBRAA
PUBLISHER IDENT.: S 0049-3848(98)00201-1
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 May 1999
Last Updated on STN: 12 May 1999

L9 ANSWER 21 OF 34 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
TI Preparation of a polysaccharide for non-invasive delivery e.g. transdermal, pulmonary delivery involves neutralizing a polysaccharide by digesting the polypeptide with at least one agent which cleaves the polysaccharide at known locations.
AN 2003-865518 [80] WPIDS
AB WO2003090696 A UPAB: 20031211
NOVELTY - Preparation (p1) of a polysaccharide for non-invasive delivery involves neutralizing a polysaccharide by digesting the polypeptide with at least one agent (A1) which cleaves the polysaccharide at known locations in the polysaccharide based upon its chemical signature.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) preparation (p2) of a **heparin** for non-invasive in vivo delivery (preferably pulmonary, transdermal or mucosal delivery) involving neutralizing a **heparin** by digesting with at least one agent (A2) based upon the chemical signature of the **heparin**;

(2) preparation (p3) of a polysaccharide (preferably **heparin** -like glycosaminoglycan (HLGAG)) for non-invasive in vivo delivery involving determining a chemical signature for a polysaccharide and reducing the mass of the polysaccharide based upon its chemical signature;

(3) preparation (p4) of **heparin** (preferably **low molecular weight heparin** (LMWH)) for non-invasive in vivo delivery (preferably pulmonary, transdermal or mucosal delivery) involving determining a chemical signature for the **heparin** and reducing the mass of the **heparin** based upon its chemical signature;

(4) a composition (C1) for oral delivery of a **heparin** (preferably LMWH), where the **heparin** has a net negative charge which is less than a reference net charge for the **heparin**;

(5) a composition (C2) for pulmonary delivery of a **heparin** (preferably LMWH) comprising a **heparin** and a charge neutralizing agent, where the **heparin** has a net negative charge which is less than a reference net charge for the **heparin**;

(6) a composition for mucosal delivery comprising M405 or M108;

(7) delivering (p5) a sulfonated polysaccharide (preferably unfractionated or fractionated **heparin** selected from LMWH) to a subject involving orally administering the sulfonated polysaccharide;

(8) a method (p6) for oral delivery of **heparin** (preferably LMWH (at least 2 mg/kg)) or pulmonary delivery of **heparin** (preferably LMWH (at least 20 mg/puff) to a subject involving orally or pulmonarily administering a **heparin** having a net negative charge less than the net reference charge;

(9) a method (p7) for delivering M405 or M108 to a subject involving orally administering a composition comprising M405 or M108;

(10) a method (p8) of delivery of an HLGAG (preferably synthetic pentasaccharide selected from arixtra or its derivative or the compounds given in figure 9 of the specification) to the pulmonary system of a subject involving administering HLGAG to the pulmonary tissue of a subject to provide a preselected effect (preferably anti-Xa activity or anti-IIa activity) in the subject, where the dose of the HLGAG is at least 2 times greater than a subcutaneous or intravenous dose of the HLGAG to give the preselected effect;

(11) a composition (C3) for pulmonary delivery comprising a synthetic HLGAG (preferably arixtra or its derivative or the compounds given in

figure 9 of the specification) to provide a preselected effect (preferably anti-Xa activity or anti-IIa activity). The composition is in a device, which delivers the HLGAG at a unit dose, which is at least 2 times greater than the unit dose used for subcutaneous or intravenous delivery of the HLGAG to provide a preselected effect; and

(12) a pressurized container or dispenser comprising (C3).

ACTIVITY - Anticoagulant; Thrombolytic; Cardiovascular-Gen.; Antiarrhythmic; Vasotropic; Antiinflammatory; Antimigraine; Antiarteriosclerotic; Immunosuppressive; Dermatological; Antiallergic; Respiratory-Gen.; Antiasthmatic; CNS-Gen.; Cytostatic; Ophthalmological; Osteopathic; Antiarthritic; Antipsoriatic; Neuroprotective; Nootropic; Cardiant; Antibacterial; Cerebroprotective; Antianginal.

MECHANISM OF ACTION - Angiogenesis inhibitor; Inhibitor of neovascularization associated with eye disease; Cancer cell growth inhibitor; Angiogenesis-inhibitor; Angiogenesis stimulator.

USE - In the preparation of a polysaccharide (e.g. HLGAG) or its composition for non-invasive in vivo delivery (claimed) and for treating subjects suffering from coagulation (such as thrombosis, cardiovascular disease, vascular conditions or atrial fibrillation), migraine, atherosclerosis, inflammatory disorder (e.g. autoimmune disease or atopic disorders), allergy, respiratory disorder (e.g. asthma, emphysema, adult respiratory distress syndrome, cystic fibrosis or lung reperfusion injury), cancer or metastatic disorder, angiogenic disorder (such as neovascular disorders of the eye, osteoporosis, psoriasis, arthritis, Alzheimer's or is undergoing or having undergone surgical procedure, organ transplant, orthopedic surgery, hip replacement, knee replacement and fracture (e.g. hip fracture, percutaneous coronary intervention, stent placement, angioplasty, coronary artery bypass graft surgery) (all claimed). Also useful for the treatment of angiogenesis, thrombotic disorders, circulatory shock and related disorders. The thrombotic disorders include heart attack, stroke, deep venous thrombosis, acute coronary syndrome (e.g. unstable angina and myocardial infarcts). The vascular disorders include cerebral ischemia (e.g. stroke such as thromboembolic stroke and pulmonary embolism), deep venous thrombosis and peripheral vascular disease. The respiratory disorders include allergy, ischemia-reperfusion injury of the lung, kidney, heart and gut, and lung tumor growth and metastasis.

Dwg.0/12

ACCESSION NUMBER: 2003-865518 [80] WPIDS
DOC. NO. CPI: C2003-244850
TITLE: Preparation of a polysaccharide for non-invasive delivery e.g. transdermal, pulmonary delivery involves neutralizing a polysaccharide by digesting the polypeptide with at least one agent which cleaves the polysaccharide at known locations.
DERWENT CLASS: B04 B05 D16
INVENTOR(S): QI, Y; RICHARDSON, T; SASISEKHARAN, R; SHRIVER, Z; SUNDARAM, M; VENKATARAMAN, G
PATENT ASSIGNEE(S): (QIYY-I) QI Y; (RICH-I) RICHARDSON T; (SASI-I) SASISEKHARAN R; (SHRI-I) SHRIVER Z; (SUND-I) SUNDARAM M; (VENK-I) VENKATARAMAN G; (MOME-N) MOMENTA PHARM INC
COUNTRY COUNT: 103
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2003090696 | A2 | 20031106 | (200380)* | EN | 63 |

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA

ZM ZW
US 2004087543 A1 20040506 (200430)
AU 2003225182 A1 20031110 (200442)
EP 1551852 A2 20050713 (200546) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
JP 2006501815 W 20060119 (200606) 74

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| WO 2003090696 | A2 | | WO 2003-US13085 | 20030425 |
| US 2004087543 | A1 | Provisional | US 2002-375927P | 20020425 |
| | | Provisional | US 2002-375970P | 20020425 |
| | | Provisional | US 2002-383926P | 20020528 |
| | | Provisional | US 2002-393959P | 20020705 |
| | | Provisional | US 2003-446432P | 20030210 |
| | | | US 2003-423725 | 20030425 |
| AU 2003225182 | A1 | | AU 2003-225182 | 20030425 |
| EP 1551852 | A2 | | EP 2003-721896 | 20030425 |
| | | | WO 2003-US13085 | 20030425 |
| JP 2006501815 | W | | JP 2003-587335 | 20030425 |
| | | | WO 2003-US13085 | 20030425 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 2003225182 | A1 | Based on | WO 2003090696 |
| EP 1551852 | A2 | Based on | WO 2003090696 |
| JP 2006501815 | W | Based on | WO 2003090696 |

PRIORITY APPLN. INFO: US 2003-446432P 20030210; US 2002-375927P 20020425; US 2002-375970P 20020425; US 2002-383926P 20020528; US 2002-393959P 20020705; US 2003-423725 20030425

L9 ANSWER 22 OF 34 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
TI **Low molecular weight**, bioactive **protamine** with reduced immunoresponsiveness, useful for neutralizing **heparin** and reducing post-operative bleeding.
AN 2000-602108 [57] WPIDS
AB WO 200055196 A UPAB: 20001109
NOVELTY - A purified bioactive **protamine** with a **low molecular weight** and reduced immunoresponsiveness or toxicity compared to native **protamine**, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a method of preparing a **protamine** (as above) comprising proteolysis of native **protamine** with a proteolytic enzyme; and
(2) a method of selecting an improved **low molecular weight protamine** species or fraction comprising comparing the bioactivity and immunoresponsiveness/toxicity of the bioactive **protamine** with native **protamine**.
ACTIVITY - Antidiabetic; coagulant; anticoagulant.
No biological data given.
MECHANISM OF ACTION - **Heparin** Antagonist.
USE - The bioactive **protamine** is useful for binding or as an antagonist to **heparin** or **low molecular weight heparin**, as a coagulant or to reverse

anti-coagulant activity of **heparin** or LMW (**low molecular weight**) **heparin** and to reduce undue, excessive (e.g. associated with systemic heparinization, extracorporeal blood circulation, disease or trauma/surgery) or post-operative bleeding. Compositions comprising several bioactive protamines and optionally an additional coagulant or therapeutic protein/polypeptide, e.g. insulin (especially recombinant human insulin) may also be used. The composition may also be used to prolong adsorption of insulin, especially in treating diabetes. The bioactive **protamine** is used to inactivate (LMW) **heparin** (claimed).
Dwg.0/8

ACCESSION NUMBER: 2000-602108 [57] WPIDS
DOC. NO. CPI: C2000-180235
TITLE: **Low molecular weight**, bioactive **protamine** with reduced immunoresponsiveness, useful for neutralizing **heparin** and reducing post-operative bleeding.
DERWENT CLASS: B04 D16
INVENTOR(S): BYUN, Y; YANG, V C; BYRN, Y
PATENT ASSIGNEE(S): (UNMI) UNIV MICHIGAN; (BYUN-I) BYUN Y; (YANG-I) YANG V C
COUNTRY COUNT: 91
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2000055196 | A1 | 20000921 | (200057)* | EN | 96 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW | | | | | |
| W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW | | | | | |
| AU 2000038879 | A | 20001004 | (200101) | | |
| US 6624141 | B1 | 20030923 | (200364) | | |
| US 2005101532 | A1 | 20050512 | (200532) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| WO 2000055196 | A1 | | WO 2000-US6876 | 20000315 |
| AU 2000038879 | A | | AU 2000-38879 | 20000315 |
| US 6624141 | B1 | Provisional | US 1999-124873P | 19990317 |
| | | | WO 2000-US6876 | 20000315 |
| | | | US 2000-700967 | 20001116 |
| US 2005101532 | A1 | Provisional | US 1999-124873P | 19990317 |
| | | Div ex | WO 2000-US6876 | 20000315 |
| | | Div ex | US 2000-700967 | 20001116 |
| | | | US 2003-668663 | 20030923 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 2000038879 | A | Based on | WO 2000055196 |
| US 6624141 | B1 | Based on | WO 2000055196 |
| US 2005101532 | A1 | Div ex | US 6624141 |

PRIORITY APPLN. INFO: US 1999-124873P 19990317; US 2000-700967 20001116; US 2003-668663 20030923

L9 ANSWER 23 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN

TI Anticoagulant monitoring using a polycation-sensitive sensor and neutralization with **low molecular weight protamine**
AB Unavailable
ACCESSION NUMBER: 2004:332875 HCAPLUS
DOCUMENT NUMBER: 142:141155
TITLE: Anticoagulant monitoring using a polycation-sensitive sensor and neutralization with **low molecular weight protamine**
AUTHOR(S): Lee, Lai-Ming
CORPORATE SOURCE: Univ. of Michigan, Ann Arbor, MI, USA
SOURCE: (2003) 120 pp. Avail.: UMI, Order No. DA3096137 From: Diss. Abstr. Int., B 2003, 64(6), 2685
DOCUMENT TYPE: Dissertation
LANGUAGE: English

L9 ANSWER 24 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
TI A Less Toxic **Heparin** Antagonist-**Low Molecular Weight Protamine**
AB A new thirteen amino acid peptide, named low mol. weight **protamine** (LMWP), was obtained through the enzymic digestion of native **protamine**. Both in vitro and in vivo results showed that LMWP fully maintained the **heparin** neutralization function of **protamine** but had much lower immunogenicity and antigenicity. Unlike **protamine**, neither LMWP nor LMWP/**heparin** complexes caused significant blood platelet aggregation in rats. These results suggest that LMWP can be used as a substitute for **protamine** for developing a new generation of nontoxic **heparin** antagonists.
ACCESSION NUMBER: 2003:70977 HCAPLUS
DOCUMENT NUMBER: 139:173469
TITLE: A Less Toxic **Heparin** Antagonist-**Low Molecular Weight Protamine**
AUTHOR(S): Liang, J. F.; Zhen, L.; Chang, L.-C.; Yang, V. C.
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109-1065, USA
SOURCE: Biochemistry (Moscow, Russian Federation)(Translation of Biokhimiya (Moscow, Russian Federation)) (2003), 68(1), 116-120
CODEN: BIORAK; ISSN: 0006-2979
PUBLISHER: MAIK Nauka/Interperiodica Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 25 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
TI **Low molecular weight protamine** as nontoxic **heparin/low molecular weight heparin** antidote. (III): Preliminary in vivo evaluation of efficacy and toxicity using a canine model
AB **Heparin** employed in cardiovascular surgeries often leads to a high incidence of bleeding complications. **Protamine** employed in **heparin** reversal, however, can cause severe adverse reactions. In an attempt to address this clin. problem, we developed low mol. weight **protamine** (LMWP) as a potentially effective and less toxic **heparin** antagonist. A homogeneous 1880-d peptide fragment, termed LMWP-TDSP5 and containing the amino acid sequence of VSRRRRRRGGRRRR, was derived directly from **protamine** by enzymic digestion of **protamine** with thermolysin. In vitro studies demonstrated that TDSP5 was capable of neutralizing various anticoagulant functions of both **heparin** and com. low-mol.-weight **heparin** prepns. In addition, TDSP5 exhibited significantly reduced cross reactivity toward mouse sera

containing anti-**protamine** antibodies. TDSP5 showed a decrease in its potential in activating the complement system. All of these findings suggested the possibility of markedly reduced **protamine** toxicity for TDSP5.

ACCESSION NUMBER: 2001:758900 HCAPLUS
DOCUMENT NUMBER: 137:27995
TITLE: **Low molecular weight protamine** as nontoxic **heparin/low molecular weight heparin** antidote. (III): Preliminary in vivo evaluation of efficacy and toxicity using a canine model
AUTHOR(S): Lee, Lai Ming; Chang, Li-Chien; Wrobleski, Shirley; Wakefield, Thomas W.; Yang, Victor C.
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109, USA
SOURCE: PharmSci [online computer file] (2001), 3(3), No pp. given
CODEN: PHARFY; ISSN: 1522-1059
URL: http://www.pharmsci.org/scientificjournals/pharmsci/journal/01_19.html
PUBLISHER: American Association of Pharmaceutical Scientists
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 26 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
TI **Low molecular weight protamine** (LMWP) as nontoxic **heparin/low molecular weight heparin** antidote. (II): In vitro evaluation of efficacy and toxicity
AB Patients undergoing anticoagulation with **heparin** or low-mol.-weight **heparin** (LMWH) require a superior antidote that possesses more selective biol. actions and a better safety profile than **protamine**. We had previously developed 2 low-mol.-weight **protamine** (LMWP) fractions (TDSP4 and TDSP5) from thermolysin-digested **protamine** as potential nontoxic, **heparin**-neutralizing agents. In this, the second article in this series, studies focused on in vitro evaluation of **heparin**/LMWH-neutralizing efficacy and putative toxicity. These LMWP fractions, particularly TDSP5, were effective and fully capable of neutralizing a broad spectrum of **heparin**-induced anticoagulant activities (i.e., aPTT, anti-Xa, and anti-IIa activities). Addnl., these LMWP fractions could neutralize the activities of com. LMWH. As assessed by the anti-Xa assay, TDSP5 was as effective as, although less potent than, **protamine** in reversing the activity of Mono-Embolex (mol. weight 5000-7000) and 2 other different sizes (mol. weight of 3000 and 5000 D) of LMWH prepns. Furthermore, compared with **protamine**, TDSP5 exhibited a much-reduced toxicity and thus an improved safety profile, as reflected by its reduced ability to activate the complement system and cross-react with the anti-**protamine** antibodies, which are 2 primary indexes of **protamine** toxicity.

ACCESSION NUMBER: 2001:758885 HCAPLUS
DOCUMENT NUMBER: 137:27994
TITLE: **Low molecular weight protamine** (LMWP) as nontoxic **heparin/low molecular weight heparin** antidote. (II): In vitro evaluation of efficacy and toxicity
AUTHOR(S): Chang, Li-Chien; Liang, Jun Feng; Lee, Hsiao-Feng; Lee, Lai Ming; Yang, Victor C.
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109, USA

SOURCE: PharmSci [online computer file] (2001), 3(3), No pp. given
CODEN: PHARFY; ISSN: 1522-1059
URL: http://www.pharmsci.org/scientificjournals/pharmsci/journal/01_18.html
PUBLISHER: American Association of Pharmaceutical Scientists
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 27 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
TI **Low molecular weight protamine** (LMWP) as nontoxic **heparin/low molecular weight heparin** antidote. (I): Preparation and characterization
AB Low-mol.-weight **protamine** (LMWP) appears to be a promising solution for **heparin** neutralization without the **protamine** -associated catastrophic toxic effects. The feasibility of this hypothesis was proven previously by using a peptide mixture produced from proteolytic digestion of **protamine**. To further examine the utility of this compound as an ultimate nontoxic **protamine** substitute, detailed studies on the purification and characterization of LMWP including the precise amino acid sequence, structure-function relationship, and possible mechanism were conducted. A number of LWMP fragments, composed of highly cationic peptides with mol. wts. ranging from 700 to 1900 D, were prepared by digestion of native **protamine** with the protease thermolysin. These fragments were fractionated using a **heparin** affinity chromatog., and their relative binding strengths toward **heparin** were elucidated. Five distinct fractions were eluted at NaCl concentration ranging from 0.4 to 1.0 M and were denoted as TDSP1 to TDSP5, in increasing order of eluting ionic strength. Among these 5 fractions, TDSP4 and TDSP5 contained 3 LMWP peptide fragments, and they were found to retain the complete **heparin**-neutralizing function of **protamine**. By using a peptide mass spectrometry (MS) fingerprint mapping technique, the amino acid sequences of the microheterogeneous LMWP fragments in all these 5 elution fractions were readily identified. A typical structural scaffold made by arginine clusters in the middle and non-arginine residues at the N-terminal of the peptide sequence was observed for all these LMWP fragments. By aligning the sequences with the potency in **heparin** neutralization of these LMWP fragments, it was found that retention of potency similar to that of **protamine** required the presence of at least 2 arginine clusters in the LMWP fragments; such as the sequence of VSRRRRRRGGRRRR seen in the most potent LMWP fraction-TDSP5. The above finding was further validated by using a synthetic LMWP analog, CRRRRRRR, and it was found that its **heparin** -neutralizing ability was increased by changing from a monomeric to a dimeric structure of this analog peptide. Based on these results, the structural requirement for a compound to function as an effective **heparin** antidote and the possible mechanism involved in **heparin** neutralization were established.
ACCESSION NUMBER: 2001:758852 HCAPLUS
DOCUMENT NUMBER: 137:27993
TITLE: **Low molecular weight protamine** (LMWP) as nontoxic **heparin/low molecular weight heparin** antidote. (I): Preparation and characterization
AUTHOR(S): Chang, Li-Chien; Lee, Hsiao-Feng; Yang, ZhiQiang; Yang, Victor C.
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109, USA
SOURCE: PharmSci [online computer file] (2001), 3(3), No pp.

given
CODEN: PHARFY; ISSN: 1522-1059
URL: http://www.pharmsci.org/scientificjournals/pharmsci/journal/01_17.html
PUBLISHER: American Association of Pharmaceutical Scientists
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 28 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
TI Reduced Reactivity Towards Anti-**Protamine** Antibodies of a **Low Molecular Weight Protamine** Analogue
AB The authors previous study showed that a low mol. weight **protamine** (LMWP) analog derived from native **protamine** could completely neutralize the anticoagulant functions of **heparin** and yet did not yield cross-reactivity towards mouse anti-**protamine** antibodies. Preliminary results presented in this short communication further confirm this lack of reactivity of LMWP towards human anti-**protamine** antibodies, using sera obtained from diabetic patients with prior sustained exposure to **protamine**-containing insulin. This finding is of clin. significance, since it may allow LMWP to be used safely in **heparin** reversal following cardiovascular surgeries without the concern of eliciting any possible life-threatening, **protamine**-induced anaphylactic responses.
ACCESSION NUMBER: 2001:259330 HCAPLUS
DOCUMENT NUMBER: 135:86873
TITLE: Reduced Reactivity Towards Anti-**Protamine** Antibodies of a **Low Molecular Weight Protamine** Analogue
AUTHOR(S): Tsui, B.; Singh, V. K.; Liang, J. F.; Yang, V. C.
CORPORATE SOURCE: College of Pharmacy, University of Michigan, Ann Arbor, MI, 48109-1065, USA
SOURCE: Thrombosis Research (2001), 101(5), 417-420
CODEN: THBRAA; ISSN: 0049-3848
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 29 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
TI **Low molecular weight protamine**. A potent but nontoxic antagonist to **heparin/low molecular weight protamine**
AB To avoid bleeding complications, **protamine** is routinely used after cardiovascular surgery to neutralize the anticoagulant function of **heparin**. However, its clin. use is associated with adverse and sometimes fatal reactions. Based on literature review of the mechanism of **heparin** neutralization and **protamine** induced immunol. toxicity, the authors propose the following hypothesis. If a chain shortened low mol. weight **protamine** (LMWP) containing the **heparin** neutralizing domain could be derived from native **protamine**, it could be a potent and yet nontoxic **heparin** antagonist. In this study, we present results to validate this hypothesis. LMWP fragments containing an intact arginine sequence and an average mol. weigh of approx. 1,100 daltons were successfully prepared by enzymic digestion of **protamine** with thermolysin. In vitro studies show that such LMWP fragments completely neutralized the anticoagulant functions of **heparin** and LMWH, based on the anti-Xa chromogenic and aPTT clotting time assays. In vivo results reveal that although

injection of **protamine** to mice led to obvious production of anti-**protamine** antibodies, injection of LMWP did not elicit any detectable immunogenic responses. In addition, these LMWP fragments exhibited a markedly reduced antigenicity and cross-reactivity toward the mice anti-**protamine** antibodies.

ACCESSION NUMBER: 2000:549612 HCAPLUS
DOCUMENT NUMBER: 134:80644
TITLE: **Low molecular weight protamine**. A potent but nontoxic antagonist to **heparin/low molecular weight protamine**
AUTHOR(S): Byun, Youngro; Chang, Li-Chien; Lee, Lai-Ming; Han, In Suk; Singh, Vijendra K.; Yang, Victor C.
CORPORATE SOURCE: College of Pharmacy, University of Michigan, Ann Arbor, MI, USA
SOURCE: ASAIO Journal (2000), 46(4), 435-439
CODEN: AJOUET; ISSN: 1058-2916
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 30 OF 34 HCAPLUS COPYRIGHT 2006 ACS on STN
TI **Low molecular weight protamine**: a potential nontoxic **heparin** antagonist
AB **Protamine** sulfate is the universal clin. antagonist to **heparin** and is used routinely after cardiovascular surgery to neutralize the anticoagulant function of **heparin**. Its clin. use, however, is associated with adverse effects including idiosyncratic fatal reactions. An examination of the mechanism of **heparin** neutralization and **protamine** toxicity suggests that the reversal of **heparin** anticoagulation may only require a small arginine-rich fragment of **protamine** to electrostatically dissociate antithrombin III from its binding to a specific pentasaccharide sequence in **heparin**. A review of literature indicates that chain-shortened peptide fragments derived from their parent proteins are normally accompanied with significantly reduced antigenicity and immunogenicity, which are two primary contributing factors to **protamine**-induced life-threatening toxic effects via an Ig-mediated pathway. Based on these observations, the authors propose the authors general hypothesis: if a chain-shortened low mol. weight **protamine** (LMWP) fragment containing the **heparin** -neutralizing domain could be derived directly from a native **protamine**, it could be a potent and nontoxic **heparin** antagonist. In this article, the authors present the authors exptl. results to support the above hypothesis. LMWP fragments containing an intact arginine sequence and an average mol. weigh of approx. 1.1 kDa were prepared successfully by enzymic digestion of native **protamine** with thermolysin. In vitro studies demonstrated that such LMWP fragments completely neutralized the anticoagulant functions of **heparin**, based on the anti-Xa chromogenic assay and aPTT clotting time assay. The authors in vivo results indicated that while administration of **protamine** to mice led to obvious production of antiprotamine antibodies, injection of LMWP did not elicit any detectable immunogenic responses. In addition, the LMWP fragments showed a significantly reduced antigenicity or, in other words, cross-reactivity towards the mice antiprotamine antibodies produced by the administration of **protamine**.

ACCESSION NUMBER: 1999:203002 HCAPLUS
DOCUMENT NUMBER: 131:13674
TITLE: **Low molecular weight protamine**: a potential nontoxic

**heparin** antagonist
AUTHOR(S): Byun, Youngro; Singh, Vijendra K.; Yang, Victor C.
CORPORATE SOURCE: Department of Pharmaceutics, College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48105-1069, USA
SOURCE: Thrombosis Research (1999), 94(1), 53-61
CODEN: THBRAA; ISSN: 0049-3848
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 31 OF 34 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI The minimal functional sequence of **protamine**.
AB Despite its nearly universal applications, **protamine**, a mixture of four major peptides with different sequences, is associated with clinically significant side effects. Through a well-designed enzyme digestion method, various **low molecular weight** prolamine peptides were obtained. Among them, two **low molecular weight** prolamine peptides with the same or even more potent **heparin** neutralization abilities as native prolamine were identified through both in vitro and in vivo tests. In addition, in vivo experiments showed that compared to native prolamine, these two **low molecular weight** **protamine** peptides were less toxic and would be safer for clinical use. (c) 2005 Elsevier Inc. All rights reserved.
ACCESSION NUMBER: 2005:557235 BIOSIS
DOCUMENT NUMBER: PREV200510335020
TITLE: The minimal functional sequence of **protamine**.
AUTHOR(S): Liang, Jun Feng [Reprint Author]; Yang, Victor C.; Vaynshteyn, Yekaterina
CORPORATE SOURCE: Stevens Inst Technol, Dept Chem and Biol Chem, Hoboken, NJ 07030 USA
SOURCE: Biochemical and Biophysical Research Communications, (OCT 21 2005) Vol. 336, No. 2, pp. 653-659.
CODEN: BBRCA9. ISSN: 0006-291X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Dec 2005
Last Updated on STN: 7 Dec 2005

L9 ANSWER 32 OF 34 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI A less toxic **heparin** antagonist: **Low molecular weight protamine**.
AB A new thirteen amino acid peptide, named **low molecular weight protamine** (LMWP), was obtained through the enzymatic digestion of native **protamine**. Both in vitro and in vivo results showed that LMWP fully maintained the **heparin** neutralization function of **protamine** but had much lower immunogenicity and antigenicity. Unlike **protamine**, neither LMWP nor LMWP/**heparin** complexes caused significant blood platelet aggregation in rats. These results suggest that LMWP can be used as a substitute for **protamine** for developing a new generation of nontoxic **heparin** antagonists.
ACCESSION NUMBER: 2003:201967 BIOSIS
DOCUMENT NUMBER: PREV200300201967
TITLE: A less toxic **heparin** antagonist: **Low molecular weight protamine**.
AUTHOR(S): Liang, J. F. [Reprint Author]; Zhen, L.; Chang, L.-C.; Yang, V. C.
CORPORATE SOURCE: College of Pharmacy, The University of Michigan, 428 Church

str., Ann Arbor, MI, 48109-1065, USA
junfeng@umich.edu
SOURCE: Biochemistry (Moscow), (January 2003) Vol. 68, No. 1, pp. 116-120. print.
CODEN: BIORAK. ISSN: 0006-2979.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Apr 2003
Last Updated on STN: 23 Apr 2003

L9 ANSWER 33 OF 34 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

TI **Low molecular weight protamine**: A potential nontoxic **heparin** antagonist.

AB **Protamine** sulfate is the universal clinical antagonist to **heparin** and is used routinely after cardiovascular surgery to neutralize the anticoagulant function of **heparin**. Its clinical use, however, is associated with adverse effects including idiosyncratic fatal reactions. An examination of the mechanism of **heparin** neutralization and **protamine** toxicity suggests that the reversal of **heparin** anticoagulation may only require a small arginine-rich fragment of **protamine** to electrostatically dissociate antithrombin III from its binding to a specific pentasaccharide sequence in **heparin**. A review of literature indicates that chain-shortened peptide fragments derived from their parent proteins are normally accompanied with significantly reduced antigenicity and immunogenicity, which are two primary contributing factors to **protamine**-induced life-threatening toxic effects via an immunoglobulin-mediated pathway. Based on these observations, we propose our general hypothesis: if a chain-shortened **low molecular weight protamine** fragment containing the **heparin**-neutralizing domain could be derived directly from a native **protamine**, it could be a potent and nontoxic **heparin** antagonist. In this article, we present our experimental results to support the above hypothesis. LMWP fragments containing an intact arginine sequence and an average molecular weigh of approximately 1.1 kDa were prepared successfully by enzymatic digestion of native **protamine** with thermolysin. In vitro studies demonstrated that such LMWP fragments completely neutralized the anticoagulant functions of **heparin**, based on the anti-Xa chromogenic assay and aPTT clotting time assay. Our in vivo results indicated that while administration of **protamine** to mice led to obvious production of antiprotamine antibodies, injection of LMWP did not elicit any detectable immunogenic responses. In addition, the LMWP fragments showed a significantly reduced antigenicity or, in other words, cross-reactivity towards the mice antiprotamine antibodies produced by the administration of **protamine**.

ACCESSION NUMBER: 1999:216698 BIOSIS
DOCUMENT NUMBER: PREV199900216698
TITLE: **Low molecular weight protamine**: A potential nontoxic **heparin** antagonist.
AUTHOR(S): Byun, Youngro; Singh, Vijendra K.; Yang, Victor C. [Reprint author]
CORPORATE SOURCE: College of Pharmacy, University of Michigan, 428 Church Street, Ann Arbor, MI, 48105-1069, USA
SOURCE: Thrombosis Research, (April 1, 1999) Vol. 94, No. 1, pp. 53-61. print.
CODEN: THBRAA. ISSN: 0049-3848.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 May 1999
Last Updated on STN: 26 May 1999

L9 ANSWER 34 OF 34 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
TI The minimal functional sequence of **protamine**; **low molecular weight protamine** peptide sequence preparation via well-designed enzyme digestion method for use in gene therapy
AN 2005-27150 BIOTECHDS
AB AUTHOR ABSTRACT - Despite its nearly universal applications, **protamine**, a mixture of four major peptides with different sequences, is associated with clinically significant side effects. Through a well-designed enzyme digestion method, various **low molecular weight** prolamine peptides were obtained. Among them, two **low molecular weight** prolamine peptides with the same or even more potent **heparin** neutralization abilities as native prolamine were identified through both in vitro and in vivo tests. In addition, in vivo experiments showed that compared to native prolamine, these two **low molecular weight protamine** peptides were less toxic and would be safer for clinical use. (c) 2005 Elsevier Inc. All rights reserved. (7 pages)
ACCESSION NUMBER: 2005-27150 BIOTECHDS
TITLE: The minimal functional sequence of **protamine**; **low molecular weight protamine** peptide sequence preparation via well-designed enzyme digestion method for use in gene therapy
AUTHOR: LIANG JF; YANG VC; VAYNSHTEYN Y
CORPORATE SOURCE: Stevens Inst Technol; Tianjin Univ; Univ Michigan
LOCATION: Liang JF, Stevens Inst Technol, Dept Chem and Biol Chem, Hoboken, NJ 07030 USA
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS; (2005) 336, 2, 653-659
ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English